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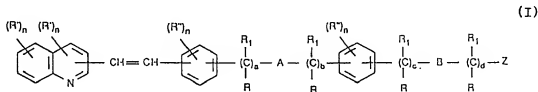
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International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁴ : C07D 215/12, 215/14, 215/22 C07D 401/10	A1	(11) International Publication Number: WO 89/12629
		(43) International Publication Date: 28 December 1989 (28.12.89)
<p>(21) International Application Number: PCT/US89/02692</p> <p>(22) International Filing Date: 20 June 1989 (20.06.89)</p> <p>(30) Priority data: 210,468 20 June 1988 (20.06.88) US</p> <p>(60) Parent Application or Grant (63) Related by Continuation US 210,468 (CIP) Filed on 20 June 1988 (20.06.88)</p> <p>(71) Applicant (for all designated States except US): RORER INTERNATIONAL (OVERSEAS) INC. [US/US]; 103 Springer Building, 3411 Silverside Road, Wilmington, DE 19810 (US).</p>		<p>(72) Inventors; and (75) Inventors/Applicants (for US only): HUANG, Fu-Chi [US/US]; 1333 Tanglewood Drive, Gwynedd, PA 19436 (US). GALEMMO, Robert, Anthony, Jr. [US/US]; 1301 Lincoln Drive, Ambler, PA 19002 (US). CAMPBELL, Henry, fluid [US/US]; 767 Hazelwood Drive, North Wales, PA 19454 (US).</p> <p>(74) Agents: BARRON, Alexis; Synnestvedt & Lechner, 1101 Market Street, Suite 2600, Philadelphia, PA 19107 (US) et al.</p> <p>(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US.</p> <p>Published With international search report.</p>

(54) Title: QUINOLINE DERIVATIVES AS ANTAGONISTS OF LEUKOTRIENE D₄



(57) Abstract

This invention relates to quinoliny compounds of general formula (I), and the use of these compounds as pharmacological agents which are lipoxygenase inhibitors and/or leukotriene antagonists possessing anti-inflammatory and anti-allergic properties and their pharmaceutical compositions and processes for this preparation.

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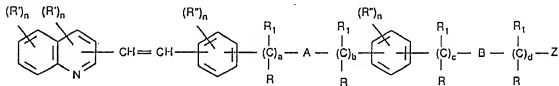
QUINOLINE DERIVATIVES AS ANTAGONISTS OF
LEUKOTRIENE D₄

Field of Invention

This invention relates to certain chemical compounds and their use as valuable pharmaceutical agents, particularly as lipxygenase inhibitors and/or leukotriene antagonists possessing anti-inflammatory and anti-allergic properties.

Summary of the Invention

This invention relates to the compounds described by the general Formula I and to therapeutic compositions comprising as active ingredient a compound of Formula I:



FORMULA I

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where

R' is independently hydrogen,
alkyl,
hydroxy,
alkoxy,
carboxy,
carbalkoxy,
halo,
nitro,
haloalkyl,
cyano or
acyl;

R_i is independently hydrogen,
alkyl or
aralkyl;

R is independently $-(CH_2)_x-X$; $-O(CH_2)_x-X$ (when not geminal
to A or B when A or B is O);
 $-S-(CH_2)_x-X$ or $-NR_1-(CH_2)_x-X$
where x is 0-3 and

X is hydrogen,
alkyl,
aryl,
hydroxy,
alkoxy,
acylamino,



-CN or
tetrazolyl;

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R" is hydrogen,
 hydroxy,
 alkoxy,
 halo,
 haloalkyl,
 $-\text{CH}_2\text{R}$; R or
 $-\text{CH}_2-\text{O}-(\text{CH}_2)_x-\text{X}$;

vicinal R groups together may be $(\text{CH}_2)_y$ - where y is 1-4,
 this forming a 3-6 membered ring;

geminal R₁ and R groups together may form a spiro
 substituent,

$-(\text{CH}_2)_z-$, where z is 2 to 5;

geminal R₁ or R₁ and R groups may together form an
 alkyldienyl substituent

A is $-\text{O}-$,

$-\text{S}-$,

$-\text{SO}-$,

$-\text{SO}-$,

$-\text{NR}_1-$,

O

$-\text{C}-$,

R₁ O

$-\text{N}-\text{C}-$,

O R₁

$-\text{C}-\text{N}-$,

R₁ R₁

$-\text{C}=\text{C}-$ or

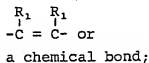
a chemical bond;

B is $-\text{O}-$,

$-\text{S}-$,

$-\text{NR}_1-$,

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a is 0-2; where a+b = 1 or 2;

b is 0-2; where a+b = 1 or 2;

c is 0-3;

d is 0-3;

n is 0-2;

Z is tetrazolyl,

substituted tetrazolyl where the substituent may be
alkyl, carboxyalkyl or carbalkoxyalkyl; or

where Y is -COOR₁,

-CN,

O

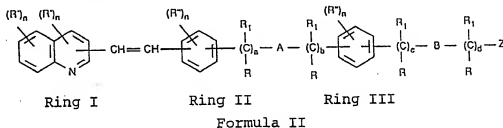
-CN(R₁)₂,

O

-CNHSO₂R₁ or-OR₁;

and pharmaceutically acceptable salts thereof.

The compounds of Formula I contain at least three aromatic rings. For the purposes of this invention these may be designated as shown in Formula II. The substitution pattern of these rings along the chain with respect to each other is as follows.

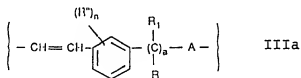


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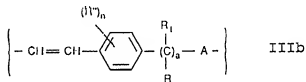
The 2-quinolinylnyl position is preferred.

The substitution pattern of the quinoline ring, that is Ring I, is at the 2-position for extending the side chain. As this side chain progresses from the quinoline ring, the two phenyl rings, designated Ring II and Ring III may be substituted along the chain in the ortho, meta or para positions with respect to each other and Ring II may also be substituted in the ortho, meta and para positions in respect to the quinoline ring.

The preferred substitution pattern for Ring II is meta or para, that is:

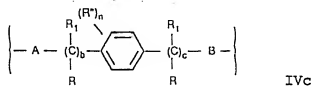
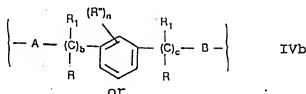
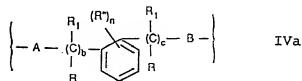


or

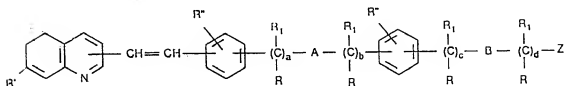


Ring III however may be substituted equally in the ortho, meta or para positions, that is:

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Further preferred compounds of this invention are described by Formula V below:

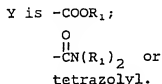


Formula V

where one of R is $-(\text{CH}_2)_x\text{-X}$; $-\text{S}-(\text{CH}_2)_x\text{-X}$; $\text{O}-(\text{CH}_2)_x\text{-X}$ (when not geminal to A or B when A or B is O); $-\text{NR}_1-(\text{CH}_2)_x\text{-X}$ or one of R' is $-\text{CH}_2\text{-O}-(\text{CH}_2)_x\text{-X}$; R or $-\text{CH}_2\text{R}$; AND R' is hydrogen or halo.

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The more preferred compounds of Formula V are those where



In addition, the present invention relates to the method of using these compounds as lipoxxygenase inhibitors and/or leukotriene antagonists possessing anti-inflammatory and anti-allergic properties.

As employed above and throughout the disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Alkyl", either alone or with various substituents defined herein, means a saturated aliphatic hydrocarbon, either branched or straight chained. A "loweralkyl" is preferred having about 1 to about 6 carbon atoms. Examples of alkyl include methyl, ethyl, n-propyl, isopropyl, butyl, sec-butyl, t-butyl, amyl, hexyl, etc.

"Alkoxy" refers to a loweralkyl-O-group.

"Alkenyl" refers to a hydrocarbon having at least one point of unsaturation and may be branched or straight chained. Preferred alkenyl groups have six or less carbon atoms present such as vinyl, allyl, ethynyl, isopropenyl, etc.

"Aralkyl" means an alkyl group substituted by an aryl radical. The preferred aralkyl groups are benzyl or phenethyl.

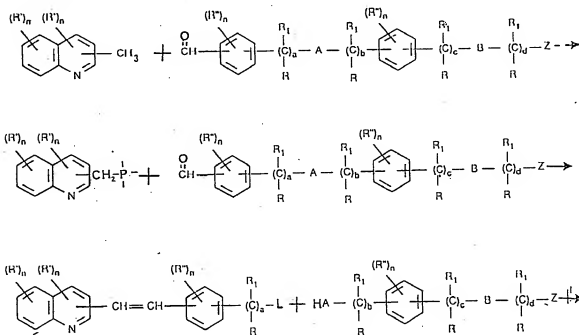
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"Cycloalkyl" means a saturated monocyclic hydrocarbon ring having 3 to about 6 carbon atoms such as cyclopropyl, cyclohexyl, etc.

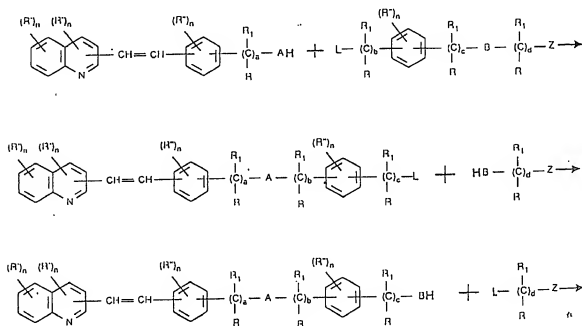
"Acyl" means an organic radical derived from an organic acid by removal of its hydroxyl group. Preferred acyl groups are acetyl, propionyl, benzoyl, etc.

"Halo" means a halogen. Preferred halogens include, chloride, bromide and fluoride. The preferred haloalkyl group is trifluoromethyl.

The compounds of this invention may be prepared in segments as is common to a long chain molecule. Thus it is convenient to synthesize these molecules by employing condensation reactions at the A, B and D sites of the molecule. For this reason the present compounds may be prepared by art recognized procedures from known compounds or readily preparable intermediates. Exemplary general procedures are as follows.



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where:

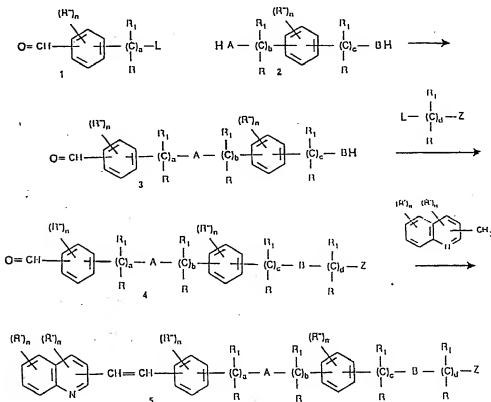
R, R', R'', R₁, a, b, c, d, n, A, and B are as defined above; Z is -CN, -CON(R₁)₂, -COOR₁ or tetrazolyl, and L is a leaving group, such as halo, tosylate, or mesylate. Where B is O or S, any base normally employed to deprotonate an alcohol or thiol may be used, such as sodium hydride, sodium hydroxide, triethyl amine, sodium bicarbonate or diisopropyl/ethylamine.

Reaction temperatures are in the range of room temperature to reflux and reaction times vary from 2 to 96 hours. The reaction is usually carried out in a solvent that will dissolve both reactants and is inert to both as well. Solvents include, but are not limited to, acetone, tetrahydrofuran, N, N-dimethyl formamide, dimethyl sulfoxide, dioxane and the like.

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More specifically and for simplicity in defining this invention further, the following exemplary procedures are shown whereby certain R, R', R'' and R₁ groups are shown as being hydrogen; a, b, c, and d are shown as being one. Of course many other combinations may be used in the practice of this invention.

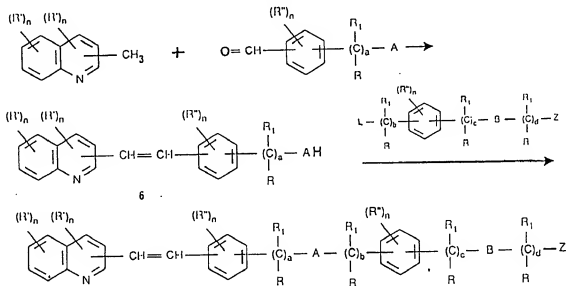
Reactions to form the 2-styryl linkage between the quinoline ring and ring II may be made at various stages of the synthesis. One such method is to form the benzaldehyde of the right hand portion of the molecule whereby the A, B and Z linkage are initially formed with rings II and III. The benzaldehyde is then reacted with the quinoline to form the desired compound.



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When the benzaldehyde (1) having an appropriate leaving group thereon is reacted with a phenol or thiophenol (2) in the presence of any strong base normally used to deprotonate in such reactions (such as K_2CO_3 in NaH) the resultant aldehyde (3) is formed. This is usually carried out in an inert solvent at raised heat. When the latter compound (3) is reacted further with a compound of the formula $L-CH_2-Z$ the chain is extended to form the desired right hand portion of the molecule (4). Heating of the aldehyde (4) with a substituted quinaldine in the presence of a dehydrating agent such as acetic anhydride produces the desired styryl product (5).

It may also be of importance to condense the quinaldine with a benzaldehyde as above at an early stage of the synthesis and then build up the right hand portion of the molecule from this point especially when the linkage at A is an oxygen or sulfur directly attached to the Ring II.



A further method of forming the styryl bondage between the quinaldine and ring II may be accomplished by reacting an appropriate quinaldine with a strong base such as lithium hexamethyldisilazane (LiHMDS) in an inert solvent at low temperature followed -- reaction of the resulting anion with

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trimethylsilylchloride, or similar agent. This trimethylsilyl adduct is further deprotonated by reaction with a strong base such as potassium hexamethyldisilazane (KHMS) at low temperature in an inert solvent such as THF. The resulting anion is reacted with a suitable benzaldehyde(2.-4.) at low temperature followed by warming to obtain the corresponding products.

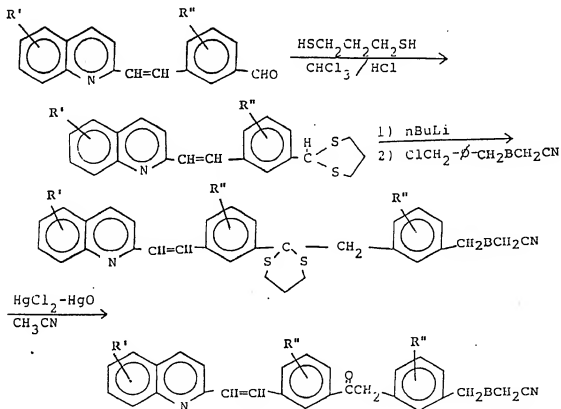
Further reactions may be carried out as previously described in order to obtain the desired compound of Formula I.

In the case where B is SO or SO₂ then treatment of the thio compound with m-chlorobenzoic acid or sodium periodate results in the sulfinyl compound. Preparation of the sulfonyl compound may be accomplished by known procedures

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such as dissolving the sulfinyl compound in acetic acid and treating with 30% H_2O_2 .

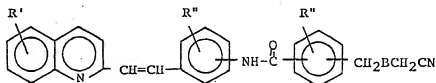
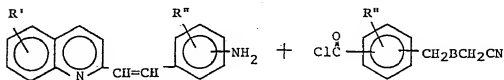
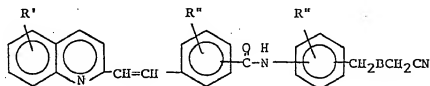
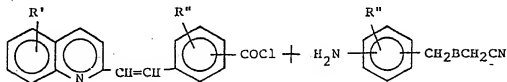
Those compounds where B is $-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-$ may be prepared by the following reaction sequence:



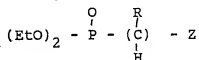
Condensation of the aldehyde with 1,3-propanedithiol results in the dithiane compound. This may be carried out in chloroform at reduced temperatures (-20°C) while bubbling HCl gas into the reaction mixture. The dithiane compound is then treated with N-butyllithium in nonpolar solvent at -78°C and then reacted with the substituted benzyl chloride. This results in addition of the Ring III to the molecule. The dithiane moiety is then treated with a mercuric chloride - mercuric oxide mixture to form the complex which is then split off leaving the desired compound.

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When B is $\begin{array}{c} R_1 \\ | \\ -N- \\ | \\ O \\ || \\ C- \end{array}$ or $\begin{array}{c} O \\ || \\ C- \\ | \\ R_1 \end{array}$ then condensation of the acid halide with the appropriate aniline will give the desired compound



Those compounds where B is $\begin{array}{c} R_1 \\ | \\ -C= \\ | \\ R_1 \end{array}$ are prepared by reacting the appropriate aldehyde or ketone with a substituted Wittig reagent of the formula



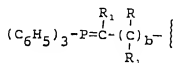
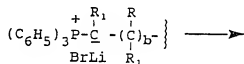
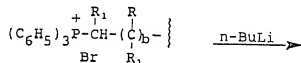
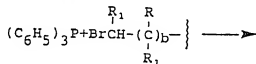
where Z is cyano or carbalkoxy.

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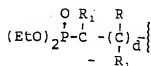
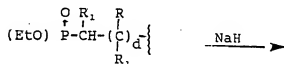
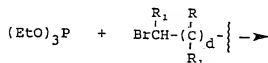
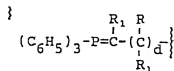
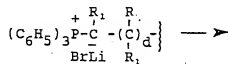
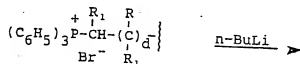
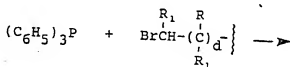
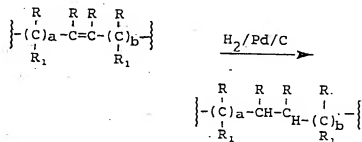
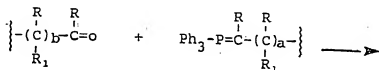
This may be carried out using normal Wittig reaction conditions. When the appropriate aldehyde or ketone is reacted with a Wittig reagent then condensation results in the formation of the double bond. This may then be reduced catalytically by known procedures such as Pd/C or any other suitable hydrogenating condition.

The Wittig reagent is prepared by known art recognized procedures such as reaction of triphenyl phosphine or diethylphosphone, with a substituted alkyl bromide followed by treatment with a strong organometallic or alkoxide base such as n-BuLi or NaOH results in the desired ylide.

Of course this Wittig condensation may also take place when the Wittig reagent is formed on Ring II position of the molecule which is then condensed with the aldehyde from the Ring III portion.



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The tetrazole may be formed from the nitrile at various stages of the synthesis by treatment with hydrazoic acid formed in situ from sodium azide and an acid.

Purification of the intermediate products and of the final products may be carried out by standard techniques such as recrystallization by solvent or chromatographic methods.

The products of this invention may be obtained as racemic mixtures of their dextro and levorotatory isomers since at least one asymmetric carbon atom may be present. When two asymmetric carbon atoms are present the product may exist as a mixture of two diastereomers based on syn and anti configurations. These diastereomers may be separated by fractional crystallization. Each diastereomer may then be resolved into dextro and levorotatory optical isomers by conventional methods. Chromatography methods also may be used.

Resolution may best be carried out in the intermediate stage where it is convenient to combine the racemic compound with an optically active compound by salt formation, ester formation, or amide formation to form two diastereomeric products. If an acid is added to an optically active base, then two diastereomeric salts are produced which possess different properties and different solubilities and can be separated by fractional crystallization. When the salts have been completely separated by repeated crystallization, the base is split off by acid hydrolysis and the pure d and l acids are obtained.

The present compounds form salts with acids when a basic amino function is present and salts with bases when an acid function, i.e., carboxyl, is present. All such salts are useful in the isolation and/or purification of the new products. Of particular value are the pharmaceutically

acceptable salts with both acids and bases. Suitable acids include, for example, hydrochloric, sulfuric, nitric, benzenesulfonic, toluenesulfonic, acetic, maleic, tartaric and the like which are pharmaceutically acceptable. Basic salts for pharmaceutical use are the Na, K, Ca and Mg salts.

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Various substituents on the present new compounds, e.g., as defined in R, R₁ and R₂ can be present in the starting compounds, added to any one of the intermediates or added after formation of the final products by known methods of substitution or conversion reactions. If the substituents themselves are reactive, then the substituents can themselves be protected according to the techniques known in the art. A variety of protecting groups known in the art, may be employed. Examples of many of these possible groups may be found in "Protective Groups in Organic Synthesis" by T. W. Green, John Wiley and Sons, 1981. For example, nitro groups can be added to the aromatic ring by nitration and the nitro group converted to other groups, such as amino by reduction, and halo by diazotization of the amino group and replacement of the diazo group. Acyl groups can be substituted onto the aryl groups by Friedel-Crafts acylation. The acyl groups can then be transformed to the corresponding alkyl groups by various methods, including the Wolff-Kishner reduction and Clemmenson reduction. Amino groups can be alkylated to form mono and dialkylamino groups; and mercapto and hydroxy groups can be alkylated to form corresponding ethers. Primary alcohols can be oxidized by oxidizing agents known in the art to form carboxylic acids or aldehydes, and secondary alcohols can be oxidized to form ketones. Thus, substitution or alteration reactions can be employed to provide a variety of substituents throughout the molecule of the starting material, intermediates, or the final product.

The compounds of the present invention have potent activity as leukotriene antagonists and as such possess therapeutic value in the treatment of inflammatory conditions and allergic responses such as anaphylaxis and asthma.

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Protocol for SRS-A (slow reacting substance of anaphylaxis) Antagonists

Leukotrienes, the products of the 5-lipoxygenase pathway of arachidonic acid metabolism, are potent contractile agents with a variety of smooth muscle preparations. Thus, it has been hypothesized that the leukotrienes contribute significantly to the pathophysiology of asthma. This protocol describes an in vitro assay used to test compounds which specifically antagonize the actions of leukotrienes.

Peripheral strips of guinea pig lungs are prepared and hung in tissue baths (Metro #ME-5505, 10 ml) according to the published procedure - (Proc. Nat'l. Acad. Sci., U.S.A. Volume 77, pp. 4354-4358, 1980). The strips are thoroughly rinsed in Assay Buffer and then connected with surgical silk thread support rods from the tissue baths. The rods are adjusted in the baths and the strips connected to the pressure transducers (Grass FT 103 or Gould US-3). The tissue baths are aerated with 95% oxygen - 5% carbon dioxide and maintained at 37°C. The assay buffer has been made as follows: for each liter of buffer the following are added to approximately 800 ml of water distilled in glass-6.87 g NaCl, 0.4 g $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$, and 2.0 g D-glucose. Then a solution of 0.368 g $\text{CaCl}_2 \cdot \text{H}_2\text{O}$ in 100 ml glass-distilled water is slowly added to the buffer. Sufficient water is added to adjust the volume to 1 liter, and the solution is aerated with 95% oxygen - 5% carbon dioxide. Usually 10 liters of buffer are used for an experiment with 4 tissues. After the tissues have been repeatedly washed and allowed to equilibrate in the tissue bath, they are challenged with 1 M histamine. After maximum contractions have been obtained, the tissues are washed, and allowed to relax back to baseline tension. This histamine challenge procedure is

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repeated at least 1 to 2 more times to obtain a repeatable control response. The average response to 1 M histamine for each tissue is used to normalize all other challenges.

Responses of each tissue to a predetermined concentration of leukotriene are then obtained. Usually test compounds are examined initially at 30 M on resting tension of the tissues without any added agonist or antagonist to determine if the compound has any possible intrinsic activity. The tissues are washed and the test compound is added again. Leukotriene is added after the desired pre-incubation time. The intrinsic activity of the compounds, and their effect on leukotriene-induced contractions are then recorded.

The results of this test for the compounds of the this invention indicates that these compounds are considered to be useful leukotriene antagonists.

Inhibitions of (^3H)-LTD₄ Binding Membranes from Guinea Pig Lung.

A. Preparation of the Crude Receptor Fraction:

This procedure was adapted from Mong *et al.* 1984). Male guinea pigs are sacrificed by decapitation and their lungs are quickly removed and placed in a beaker containing ice-cold homogenization buffer. The lungs are separated from connective tissue, minced with scissors, blotted dry and weighed. The tissue is then homogenized in 40 volumes (w/v) of homogenization buffer with a Polytron at a setting of 6 for 30 seconds. The homogenate is centrifuged at 1000 x g for 10 minutes (e.g. 3500 RPM, SS-34 Rotor). The supernate is filtered through two layers of cheese cloth and centrifuged at 30,000 x g for 30 minutes (e.g. 18,500 RPM SS-34 Rotor), after which the resulting pellet is

resuspended in 20 volumes of assay buffer by hand homogenization using a Dounce homogenizer. The final pellet is resuspended in 10 volumes of assay buffer and kept at 4°C until use.

B. Binding Assay:

Each assay tube (16 x 100 mm) contains the following:

490 µL Assay Buffer
10 µL Test compound or solvent
100 µL $^3\text{H-LTD}_4$ (ca. 17,500 DMP)
400 µL Protein preparation

Incubations are done at 25°C for 20 minutes in a shaking water bath. Reactions are started by the addition of the protein preparation. At the end of the incubation time, 4.0 ml of cold wash buffer is added to the tube. After being vortexed, the contents of the tube are immediately poured over a Whatman GF/C Filter (25 mm diameter) which is sitting in a vacuum manifold (e.g., Millipore Model No. 3025 manifold) to which a partial vacuum is applied. The filters are immediately washed with an additional 15 ml of cold buffer. The filters are transferred to 7 ml plastic scintillation vials to which 6.0 ml of appropriate scintillation fluid (e.g., Scintiverse) is added. After being allowed to equilibrate for 4-6 hours, the radioactivity is counted with a liquid scintillation counter appropriately set for tritium.

The required control assay tubes include the following:

- (a) Total Binding: No test compound is added; buffer is substituted.
- (b) Non-Specific Binding: Non-labeled ligand is added at a concentration of 1 M.

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(c) Solvent Controls: If test compound is dissolved in a solvent, controls for both Total Binding and Non-Specific Binding containing solvent but no compounds are required.

The results of this test indicate that the compounds for this invention exhibit valuable properties which are useful in the treatment of inflammatory conditions and allergic responses.

The compounds of the present invention can be administered to a mammalian host in a variety of forms adapted to the chosen route of administration, i.e., orally, or parenterally. Parenteral administration in this respect includes administration by the following routes: intravenous, intramuscular, subcutaneous, intraocular, intrasynovial, transeptheliaily including transdermal, opthalmic, sublingual and buccal; topically including opthalmic, dermal, ocular, rectal and nasal inhalation via insufflation and aerosol and rectal systemic.

The active compound may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compound may be incorporated with excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 6% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be

obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 50 and 300 mg of active compound.

The tablets, troches, pills, capsules and the like may also contain the following: A binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and formulations.

The active compound may also be administered parenterally or intraperitoneally. Solutions of the active compound as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersion can also be prepared in glycerol, liquid polyethylene glycols, and

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mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It may be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimersal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredient into a sterile vehicle which contains the basic dispersion

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medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

The therapeutic compounds of this invention may be administered to a mammal alone or in combination with pharmaceutically acceptable carriers, as noted above, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmaceutical practice.

The physician will determine the dosage of the present therapeutic agents which will be most suitable for prophylaxis or treatment and it will vary with the form of administration and the particular compound chosen, and also, it will vary with the particular patient under treatment. He will generally wish to initiate treatment with small dosages by small increments until the optimum effect under the circumstances is reached. The therapeutic dosage will generally be from 0.1 to 100 M/day or from about 0.1 mg to about 50 mg/kg of body weight per day and higher although it may be administered in several different dosage units. Higher dosages are required for oral administration.

The compounds of the present invention may be prepared by the following representative examples.

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EXAMPLE 1

2-(2-(4-Acetoxyphenyl)ethenyl)quinoline

A solution of 25g of p-hydroxybenzaldehyde and 28ml of quinaldine is 100ml of acetic anhydride are heated at 130°C overnight. The reaction mixture is concentrated in vacuo and then passed through a flash silica gel column slurry packed with hexanes and eluted with 15% acetone in hexanes. Concentration of the desired fractions gives a yellow solid which is recrystallized from Et₂O/hexanes to give 2-(2-(4-acetoxyphenyl)ethenyl)quinoline (M.P. 127-128°C).

When p-hydroxybenzaldehyde in the above procedure is replaced with p-mercaptobenzaldehyde or m-hydroxybenzaldehyde then the products prepared are 2-(2-(4-acetylthiophenyl)ethenyl)quinoline or 2-(2-(3-acetoxyphenyl)ethenyl)quinoline.

EXAMPLE 2

4-(2-(Quinolin-2-yl)ethenyl)phenol

To a suspension of 28.2g of 2-(2-(4-acetoxyphenyl)ethenyl)quinoline in 500ml of methanol is added 2.58g (0.25 equiv.) of Na₂CO₃. This is stirred for 24 hours at room temperature. To this reaction mixture is then added 200ml of pH7 buffer (25% NH₄OH) and the precipitate that forms is filtered off, washed with methanol and dried to give 4-[2-(quinolin-2-yl)ethenyl]phenol (M.P. 268-270°C).

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When 2-(2-(4-acetoxyphenyl)ethenyl)quinoline in the above procedure is replaced with 2-(2-(4-acetylthiophenyl)ethenyl)quinoline or 2-(2-(3-acetoxyphenyl)ethenyl)quinoline then the products prepared are 4-(2-(quinolin-2-yl)ethenyl)mercaptobenzene or 3-(2-(quinolin-2-yl)ethenyl)phenol.

EXAMPLE 3

2-(2-(4-(2-(Quinolin-2-yl)ethenyl)phenoxy)methyl)phenoxy)propionic acid

A. ethyl 2-(2-methylphenoxy)propionate

A mixture of 10.8g (0.1 mol) of o-cresol, 18.1g (0.1 mol) of ethyl 2-bromopropionate, and 14.5g of K_2CO_3 in 50ml of DMF is heated at 70°C for 3 days. The reaction mixture is poured into H_2O , and extracted with ethyl acetate. The organic solution is dried and evaporated to give ethyl 2-(2-methylphenoxy)propionate which is used directly in the next step.

B. ethyl 2-(2-bromomethylphenoxy)propionate

A mixture of 6g (0.029 mol) of ester obtained from step A, 5.6g (0.031 mol) of N-bromosuccinimide and 100mg of benzoyl peroxide in 100ml of CCl_4 is heated to reflux while irradiated with a sun-lamp, for 1 hour. The reaction mixture is cooled down and filtered to dryness to give ethyl 2-(2-bromomethylphenoxy)propionate which is used directly in the next step.

C. ethyl 2-(2-(4-(2-(quinolin-2-yl)ethenyl)phenoxy)methyl)phenoxy)propionate

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To a solution of 1.3g (5.23 mmol) of 4-[2-(quinolin-2-yl)ethenyl]phenol and 1.5g (5.23 mmol) of the bromide from step B in 90ml of 8:1 - acetone:DMF is added 1.52g (10.97 mmol, 2.1 equiv) of K_2CO_3 . The mixture is refluxed overnight, then partitioned between EtOAc and H_2O . The organics are dried, filtered, and concentrated in vacuo. This is then purified by flash column chromatography to give ethyl 2-(2-(4-(2-quinolin-2-yl)ethenyl)phenoxy-methyl)phenoxy)propionate as a yellow oil which is used directly in the next step.

D. 2-(2-(4-(2-(quinolin-2-yl)ethenyl)phenoxy)methyl)-phenoxy)propionic acid

To a solution of 1.20g (2.65 mmol) of the ester from step C in 25ml of EtOH is added 10ml (10.0 mmol, 3.75 equiv) of 1N NaOH. The mixture is stirred for 1 hour at room temperature which time the mixture is acidified to pH ~ 4 using 1N HCl. A precipitate forms which is filtered off and recrystallized from hot MeOH-Et₂O to afford 2-(2-(4-(2-(quinolin-2-yl)ethenyl)phenoxy)methyl)phenoxy)propionic acid in the form of a bright orange crystalline solid (M.P. = 201°-203°C).

When 4-(2-(quinolin-2-yl)ethenyl)phenol of Step C above is replaced with 4-(2-(quinolin-2-yl)ethenyl)mercaptobenzene or 3-(2-(quinolin-2-yl)ethenyl)phenol, then the products prepared are 2-(2-(4-(2-(quinolin-2-yl)ethenyl)phenyl-thiomethyl)phenoxy)propionic acid or 2-(2-(3-(2-(quinolin-2-yl)ethenyl)phenoxy)methyl)phenoxy)propionic acid.

EXAMPLE 4

When quinaldine of Example 1 is replaced by 7-chloroquinaldine or 7-bromoquinaldine and the procedures of Examples 1-3 are followed, then the products prepared are

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2-(2-(4-(2-(7-bromoquinolin-2-yl)ethenyl)phenoxy)methyl)phenoxy)propionic acid

2-(2-(4-(2-(7-chloroquinolin-2-yl)ethenyl)phenoxy)methyl)phenoxy)propionic acid

2-(2-(4-(2-(7-bromoquinolin-2-yl)ethenyl)phenylthiomethyl)phenoxy)propionic acid

2-(2-(4-(2-(7-chloroquinolin-2-yl)ethenyl)phenylthiomethyl)phenoxy)propionic acid

2-(2-(3-(2-(7-bromoquinolin-2-yl)ethenyl)phenoxy)methyl)phenoxy)propionic acid

2-(2-(3-(2-(7-bromoquinolin-2-yl)ethenyl)phenoxy)methyl)phenoxy)propionic acid

EXAMPLE 5

α -(4-(2-(7-chloroquinolin-2-yl)ethenyl)-2-(3-carboxypropoxy)phenoxy)methyl)-phenoxyacetic acid

A. 2-carboxymethoxybenzyl alcohol

A mixture of 2-hydroxybenzyl alcohol (0.5 mol), α -chloroacetic acid (0.5 mol) and solid sodium hydroxide (1.0 mol) in water (1 L) is heated at reflux for 6h. After this time the solution is cooled to ambient temperature and acidified to pH 4 with a 10% solution of hydrogen chloride in water. The product crystallizes from the acidified solution and is isolated and dried by filtration to give 2-Carboxymethoxybenzylalcohol which is used directly in the next step.

B. 2-carbomethoxymethoxybenzyl alcohol

2-Carboxymethoxybenzyl alcohol (0.4 mol) is added to a saturated solution of hydrogen chloride gas in dry methanol (800 mL). This mixture is refluxed for 8 hours after which 2-carbomethoxymethoxybenzyl alcohol is isolated by removal of the solvent and used directly in the next step.

C. 2-Carbomethoxymethoxybenzyl chloride

Thionyl chloride (0.48 mol) is added to an ether solution (1 L) containing 2-carbomethoxymethoxybenzyl alcohol (0.4. mol), and a small amount of dimethylformamide (0.5 mL). The reaction is stirred at ambient temperature for 12 h, after which it is evaporated and the residue diluted again with ether (1 L). This ether solution is washed with 2% sodium hydrogen carbonate solution (3X's) and then dried (magnesium sulfate). The solvent is removed to give 2-carbomethoxymethoxybenzyl chloride which is used directly in Step E.

D. 3-carbomethoxypropoxy-4-hydroxybenzaldehyde

Sodium hydride (0.3 mol of an 80% dispersion in mineral oil) is rinsed with dry tetrahydrofuran and stirred in dry dimethylsulfoxide (300 mL) until all of it is dissolved. 3,4-Dihydroxybenzaldehyde (0.15 mol) in dimethylsulfoxide (50 mL) is added dropwise to this solution and stirred for an additional hour after addition is complete. To the solution containing the dianion of the dihydroxybenzaldehyde methyl 4-bromobutyrate (0.15 mol) is added.

After reaction is complete the solution is poured into water and the pH adjusted to 4. The acidified aqueous layer is extracted with ethyl acetate (3X's) and the ethyl acetate extracts washed with water (6X's) and dried (MgSO₄). The solvent is removed to give 3-carbomethoxypropoxy-4-

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hydroxybenzaldehyde which is used directly in Step E.

E. 3-carbomethoxypropoxy-4-(2-(carbomethoxymethoxy)-phenyl)methyloxybenzaldehyde

A mixture of 2-carbomethoxymethoxybenzyl chloride (0.1 mol) and 3-carbomethoxypropoxy-4-hydroxybenzaldehyde (0.08 mol) in 8:1 acetone: dimethylformamide (900 mL) is refluxed with anhydrous potassium carbonate (0.1 mol). When the reaction is complete, the cooled reaction mixture is filtered and evaporated. The resulting oil is diluted with ethyl acetate and washed with water (6X's). The dried ethyl acetate solution is absorbed on silica gel and eluted through a column of flash silica (500g) with a mixture of ethyl acetate: petroleum ether. Condensation of the appropriate fraction gives 3-carbomethoxypropoxy-4-(2-(carbomethoxymethoxy)phenyl)methyloxybenzaldehyde which is used directly in the next step.

F. methyl o-(4-(2-(7-chloroquinolin-2-yl)ethenyl)-2-(3-carbomethoxypropoxy)phenoxy)methyl)phenoxyacetate

The phosphonate ester derived from 2-chloromethyl-7-chloroquinoline (0.05 mol) is added to a tetrahydrofuran (200 mL) suspension of sodium hydride (0.05 mol of an 80% dispersion in mineral oil). When gas evolution ceases 3-carbomethoxypropoxy-4-(2-(carbomethoxymethoxy)-phenyl)methyloxybenzaldehyde (0.05 mol) is added and the mixture stirred at ambient temperature. Upon consumption of the aldehyde the reaction mixture is evaporated, then diluted with ethyl acetate and washed with water. The ethyl acetate solution is dried and evaporated to give methyl o-(4-(2-(7-chloroquinolin-2-yl)ethenyl)-2-(3-carbomethoxypropoxy)-phenoxy)methyl)phenoxyacetate.

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G. o-(4-(2-(7-chloroquinolin-2-yl)ethenyl)-2-(3-carboxypropoxy)-
phenoxymethyl)phenoxyacetic acid

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The diester from Step F (0.03 mol) is dissolved in absolute ethanol (200 mL) and to this solution is added 1N sodium hydroxide solution (90 mL). More ethanol is added (ca 100 mL) to complete the solution of the diester. This mixture is stirred at ambient temperature until all of the diester is converted to the diacid which is isolated by evaporation of the reaction mixture and suspension of the resulting solids in water. The aqueous basic suspension is acidified to pH 4-5 by the addition of 10% hydrogen chloride solution. The resulting solid is filtered and is dried then recrystallized to give pure o-(4-(2-(7-chloroquinolin-2-yl)ethenyl)-2-(3-carboxypropoxy)phenoxymethyl)phenoxyacetic acid.

When 2-hydroxybenzyl alcohol is replaced by 3-hydroxybenzyl alcohol in Example 5 then the corresponding intermediate products are prepared and specifically m-(4-(2-(7-chloroquinolin-2-yl)ethenyl)-2-(3-carboxypropoxy)phenoxy-methyl)phenoxyacetic acid.

EXAMPLE 6

5-(2-(4-(2-(quinolin-2-yl)ethenyl)phenoxy-methyl)benzyl)tetr-
azole

A.2-(4-(2-(quinolin-2-yl)ethenyl)phenoxy-methyl)benzyl
chloride

A solution of 2.5g (10.11 mmol) of 4-(2-(quinolin-2-yl)ethenyl)phenol, 5.3g (30.33 mmol, 3 equiv.) of K_2CO_3 in 100 mL of 8:1 - acetone:DMF is refluxed for 24 hrs. The mixture is poured into ice-water and allowed to stand for 1 1/2 hours. The precipitate that forms is

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filtered off, redissolved in EtOAc, dried, and concentrated in vacuo. The crude product is purified by flash column chromatography to afford 2-(4-(2-(quinolin-2-yl)ethenyl)-phenoxyethyl)benzyl chloride in the form of a yellow crystalline solid: (M.P. 127° - 128° C).

B.2-(4-(2-(quinolin-2-yl)ethenyl)phenoxyethyl)-benzyl nitrile

A mixture of 1.9g (4.9 mmol) of 2-(4-(2-(quinolin-2-yl)ethenyl)phenoxyethyl)benzyl chloride 1.5g (22.3 mmol, 2equiv) of KCN, and 100mg of adogen 464 phase transfer catalyst in 70 mL of toluene and 70 mL of H₂O is refluxed for 24 hours. The reaction mixture is partitioned between EtOAc and H₂O. The organic layer is separated, dried and concentrated in vacuo to afford a brown precipitate. Recrystallization from CH₂Cl₂-pet ether gives 2-(4-(2-(quinolin-2-yl)-ethenyl)phenoxyethyl)-benzyl nitrile in the form of an orange-beige crystalline solid: (M.P. 204° - 206°C).

C.5-(2-(4-(2-(quinolin-2-yl)ethenyl)phenoxyethyl)benzyl)-tetrazole

A solution of 1.2g (3.19 mmol) of 2-(4-(2-(quinolin-2-yl)-ethenyl)phenoxyethyl)benzyl nitrile 4.1g (63.07 mmol, 20equiv) of NaN₃, and 3.4g (63.07 mmol, 20 equiv) of NH₄Cl in 20 mL of DMF is heated at 110°C for 5 days under inert atmosphere. The reaction mixture is poured into ice water and allowed to stand for 1 hour. The precipitate that forms is filtered off and redissolved in CH₂Cl₂. To this is added 1N NaOH and the sodium salt that forms is filtered off. The salt is redissolved into hot H₂O, then acidified to pH ~ 4 using 1N HCl. The precipitate that forms is filtered off, triturated with hot MeOH, and filtered to afford 5-(2-(4-(2-(quinolin-2-yl)ethenyl)phenoxyethyl)benzyl)tetrazole as a beige crystalline solid: (M.P. = 191° - 196°C).

EXAMPLE 7

2-hydroxy-3-((2-carboxyethyl)thio)-3-[2-(4-(2-(7-chloroquinolin-2-yl)ethenyl)phenoxy)methyl]phenyl]propionic acid

A. ethyl 2,3-oxido-3-(2-bromomethylphenyl)propionate

To a solution of, 5g (41.61 mmol) of o-tolualdehyde and 5.1g (41.61 mmol) of ethyl-2-chloroacetate in 10mL of EtOH at 0°C is added dropwise a solution of 0.96g (41.61 mmol) of Na in 40 mL of EtOH over a period of 15 minutes. The mixture is then stirred at room temp for 3 days. The reaction mixture is partitioned between Et₂O and H₂O. The organics are dried and concentrated in vacuo to give 5.2g of the crude epoxide as a yellow oil. This crude oil is redissolved in 100 mL of CCl₄ and to this is added 7.41g (41.61 mmol) of NBS and 20mg of benzoyl peroxide as a radical initiator. The reaction mixture is refluxed under a high intensity lamp for 1h. The reaction is cooled to 0°C and the precipitate filtered off. The filtrate is concentrated in vacuo to give a yellow oil which is purified by flash column chromatography to give ethyl 2,3-oxido-3-(2-bromomethylphenyl)-propionate in the form of a yellow oil which is used directly in the next step.

B. ethyl 2,3-oxido-3-(2-(4-(2-(7-chloroquinolin-2-yl)ethenyl)phenoxy)methyl)phenyl)propionate

A mixture of 4-(2-(7-chloroquinolin-2-yl)ethenyl)-phenol (0.01 mol), ethyl 2,3-oxido-3-(2-bromomethylphenyl)-propionate, and 0.012 mol of K₂CO₃ in 50 mL of DMF is heated at 70°C overnight. The reaction mixture is poured into H₂O, extracted with ethyl acetate. The organic layer is separated, dried and evaporated to dryness. Purification by flash chromatography gives ethyl 2,3-oxido-3-[2-(4-(2-

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(7-chloroquinolin-2-yl)ethenyl)phenoxyethyl)phenyl]propionate.

C. 2-hydroxy-3-((2-carboxyethyl)thio)-3-[2-(4-(2-(7-chloroquinolin-2-yl)ethenyl)phenoxyethyl)phenyl]propionic acid

A solution of ethyl 2,3-oxido-3-(2-(4-(2-(7-chloroquinolin-2-yl)ethenyl)phenoxyethyl)phenyl)propionate (5 mmol), ethyl mercaptopropionate (5 mmol); Et₃N (5 mmol) in 15 mL of MeOH is stirred at room temperature for 3 days. The reaction mixture is treated with 5 mmol of sodium methoxide overnight and then poured into H₂O and extracted with EtOAc. The organic solution is dried and evaporated to dryness, and the residue purified by flash chromatography. The ester is then hydrolyzed with NaOH solution, acidified with 1N HCl solution, which after purification by flash chromatography gives 2-hydroxy-3-((2-carboxyethyl)thio)-3-[2-(4-(2-(7-chloroquinolin-2-yl)ethenyl)phenoxyethyl)phenyl]propionic acid.

EXAMPLE 8

3-[2-(3-(2-(7-chloroquinolin-2-yl)ethenyl)phenyl)-1-hydroxy-2-((2-carboxyethyl)thio)ethyl]phenoxyacetic acid

3-[2-(3-(2-(7-chloroquinolin-2-yl)ethenyl)phenyl)-1-(2-carbomethoxyethyl)thio-2-hydroxyethyl]phenoxyacetic acid

A. 3-(carbomethoxymethoxy)benzyl-diethylphosphonate

Triethyl phosphonate (0.2 mol) is added to a toluene solution of 3-carbomethoxymethoxybenzylchloride (0.2 mol) and the mixture is heated at reflux. Upon the consumption of the chloride, the cooled reaction mixture is washed with dilute hydrogen chloride solution then bicarbonate solution and brine. The toluene solution is dried (magnesium sulfate)

and evaporated to give 3-(carbomethoxymethoxy)benzyl diethylphosphonate which is used directly in the next step.

B. 3-(2-(3-(carbomethoxymethoxy)phenyl)ethenyl)benzaldehyde

The diethyl phosphonate from step A (0.18 mol) is added to sodium hydride (0.18 mol of an 80% dispersion in mineral oil) suspended in tetrahydrofuran (400 mL). After the cessation of gas evolution 1,3 diformylbenzene (0.25 mol) is added in one portion to the reaction mixture. This solution is stirred until all the phosphonate is consumed then the solvent is removed and the residue diluted with ethyl acetate. The ethyl acetate solution is washed successively with dilute hydrogen chloride solution, sodium bicarbonate solution and brine. The dried ethyl acetate solution is evaporated and the residue applied to a column (0.5 Kg of flash silica gel). The mono-olefination product 3-(2-(3-(carbomethoxymethoxy)phenyl)ethenyl)benzaldehyde is isolated by elution with a mixture of ethyl acetate and petroleum ether and this is used directly in the next step.

C. 3-(1,2-oxido-2-(3-carbomethoxymethoxyphenyl)ethyl)-benzaldehyde

m-Chloroperbenzoic acid (0.11 mol) is added to a cooled (-10°C) dichloromethane solution (300 mL) of 3-(2-(3-(carbomethoxymethoxy)phenyl)ethenyl)benzaldehyde (0.1 mol) in the presence of solid sodium bicarbonate (ca ~5g). The reaction is maintained at 10°C for several hours then allowed to thaw to ambient temperature to reach completion. The dichloromethane solution is filtered, then washed twice with dilute sodium bisulfite solution followed by saturated potassium carbonate. The organic layer is dried (magnesium sulfate) and evaporated to give 3-(1,2-oxido-2-(3-carbomethoxymethoxyphenyl)ethyl)benzaldehyde which is used directly in the next step.

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D. 3-(1-((2-carbomethoxyethyl)thio)-2-hydroxy-2-(3-carbomethoxymethoxyphenyl)ethyl)benzaldehyde

3-(1-hydroxy-2-((2-carbomethoxyethyl)thio)-2-(3-carbomethoxymethoxyphenyl)ethyl)benzaldehyde

The epoxide of Step C (0.08 mol) and methyl 3-thiolpropionate (0.08 mol) in dichloromethane (300 mL) are stirred at ambient temperature. Thin layer chromatography reveals the presence of two products upon completion of the reaction. After removal of solvent the products are separated by flash chromatography with mixtures of ethyl acetate and petroleum ether to obtain 3-(1-((2-carbomethoxyethyl)thio)-2-hydroxy-2-(3-carbomethoxymethoxyphenyl)ethyl)benzaldehyde and 3-(1-hydroxy-2-((2-carbomethoxyethyl)thio)-2-(3-carbomethoxymethoxyphenyl)ethyl)benzaldehyde.

E. 7-chloroquinolin-2-yl-methyldiethylphosphonate

The diethylmethylphosphonate of 2-chloromethyl-7-chloroquinoline is prepared by refluxing equimolar amounts of 2-chloromethyl-7-chloroquinoline and triethylphosphonate in toluene. Upon completion of the reaction the cooled toluene solution is washed with water dried and evaporated to give 7-chloroquinolin-2-yl-methyl-diethylphosphonate which is used directly in Steps F and H.

F. methyl 3-[2-(3-(2-(7-chloroquinolin-2-yl)ethenyl)-phenyl)1-hydroxy-2-((2-carbomethoxyethyl)thio)ethyl]-phenoxyacetate

The phosphonate derived from 2-chloromethyl-6-chloroquinoline from Step E (0.02 mol) is added to a suspension of sodium hydride (0.04 mol from an 80% dispersion in mineral oil) in tetrahydrofuran. Upon cessation of gas evolution 3-(1-((2-carbomethoxyethyl)thio)-2-hydroxy-2-(3-carbomethox-

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y-methoxyphenyl)ethyl)benzaldehyde (0.02 mol) is added and the mixture stirred at ambient temperature until consumed.

The tetrahydrofuran solution is evaporated and the residue diluted with ethyl acetate. The ethyl acetate solution is washed with dilute hydrogen chloride solution and saturated sodium bicarbonate. After drying (magnesium sulfate) methyl 3-[2-(3-(2-(7-chloroquinolin-2-yl)ethenyl)phenyl)-1-hydroxy-2-((2-carbomethoxyethyl)thio)ethyl]-phenoxyacetate is isolated by removal of the solvent.

G. 3-[2-(3-(2-(7-chloroquinolin-2-yl)ethenyl)phenyl)-1-hydroxy-2-((2-carboxyethyl)thio)ethyl]phenoxyacetic acid

To an ethanolic solution (100 mL) of the diester from Step F (0.01 mol) is added 1N sodium hydroxide solution (30 mL). This mixture is stirred at ambient temperature until all of the diester is converted to the diacid. The product is isolated and purified by first removing the solvent then resuspending the solidified residue in water. This basic suspension is then made acid (pH 4 to 5) with dilute hydrogen chloride solution and the resulting solid isolated by filtration and air dried. This is then purified further by recrystallization to obtain pure 3-[2-(3-(2-(7-chloroquinolin-2-yl)ethenyl)phenyl)-1-hydroxy-2-((2-carboxyethyl)thio)ethyl]phenoxyacetic acid.

H. methyl 3-[2-(3-(2-(7-chloroquinolin-2-yl)ethenyl)phenyl)-1-(2-carbomethoxyethyl)thio-2-hydroxyethyl]phenoxyacetate

Following the procedure of Step F but replacing 3-(1-((2-carbomethoxyethyl)thio)-2-hydroxy-2-(3-carbomethoxy-methoxyphenyl)ethyl)benzaldehyde with 3-(1-hydroxy-2-((2-carbomethoxyethyl)thio)-2-(3-carbomethoxymethoxyphenyl)-ethyl)benzaldehyde the product prepared is methyl 3-[2-(3-(2-(7-chloroquinolin-2-yl)ethenyl)phenyl)-1-((2-carbomethoxyethyl)thio)-2-hydroxyethyl]phenoxyacetate.

I. 3-[3-(2-(7-chloroquinolin-2-yl)ethenyl)phenyl]-1-(2-carboxymethoxyethyl)thio-2-hydroxyethyl]phenoxyacetic acid

Following the procedure of Step G but replacing methyl 3-[2-(3-(2-(7-chloroquinolin-2-yl)ethenyl)phenyl)-1-hydroxy-2-((2-carbomethoxyethyl)thio)ethyl]phenoxyacetate with methyl 3-[2-(3-(2-(7-chloroquinolin-2-yl)ethenyl)phenyl)-1-(2-carbomethoxyethyl)thio-2-hydroxyethyl]phenoxyacetate the product prepared is 3-[3-(2-(7-chloroquinolin-2-yl)ethenyl)phenyl]-1-(2-carboxymethoxyethyl)thio-2-hydroxyethyl]phenoxyacetic acid.

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EXAMPLE 9

ethyl 4-(2-(4-(2-(7-chloroquinolin-2-yl)ethenyl)phenoxy-methyl)phenoxy)-4-carbethoxybutyrate

4-(2-(4-(2-(7-chloroquinolin-2-yl)ethenyl)phenoxyethyl)phenoxy)-4-carboxybutyric acid

A. ethyl 4-carbethoxy-4-(2-methylphenoxy)butyrate

A mixture of o-cresol (0.1 mol) and diethyl 2-bromoglutarate (0.1 mol) and K_2CO_3 (0.11 mol) in 50 mL of DMF are heated at 70°C overnight. The reaction is poured into water and extracted with ethyl acetate. The organic solution is washed with water, 0.1 N NaOH solution, dried and evaporated to give ethyl 4-carbethoxy-4-(2-methylphenoxy)butyrate which is used directly in the next step.

B. 2-(1,3-dicarbethoxypropoxy)benzyl bromide

A mixture of ethyl 4-carbethoxy-4-(2-methylphenoxy)butyrate (0.05 mol) and NBS (0.055 mol) and 150 mg of benzoyl peroxide in 150 mL of CCl_4 is refluxed and shined with a sun lamp for 2 hours. Filtration and evaporation of solvent gives 2-(1,3-dicarbethoxypropoxy) benzyl bromide which is used without purification.

C. ethyl 4-(2-(4-(2-(7-chloroquinolin-2-yl)ethenyl)phenoxy-methyl)phenoxy)-4-carbethoxybutyrate

4-(2-(4-(2-(7-chloroquinolin-2-yl)ethenyl)phenoxyethyl)phenoxy)-4-carboxybutyric acid

A mixture of 4-(2-(7-chloroquinolin-2-yl)ethenyl)phenol (0.01 mol) and 0.011 mol of K_2CO_3 in 50 mL of DMF are heated at 70°C overnight. The reaction mixture is poured into water

followed by extraction with ethyl acetate. The organic solution is washed with water, dried and evaporated to dryness.

The crude product is purified by column chromatography to give ethyl 4-(2-(4-(2-(7-chloroquinolin-2-yl)ethenyl)-phenoxy)methyl)phenoxy)-4-carbethoxybutyrate. The ester is treated with 1N NaOH solution (30 mL) in dioxane overnight. The reaction mixture is then acidified, and purified by flash chromatography which gives 4-(2-(4-(2-(7-chloroquinolin-2-yl)ethenyl)phenoxy)methyl)phenoxy)-4-carboxybutyric acid.

EXAMPLE 10

When the procedure of Example 9 is followed and diethyl 2-bromoglutamate is replaced by the compounds of Table I below, then the corresponding product is prepared.

Table I

diethyl 2-bromomalonate
diethyl 2-bromosuccinate
diethyl 2-bromoglutarate
diethyl 3-bromoglutarate
diethyl 2-bromoadipate
diethyl 3-bromoadipate
ethyl 2-bromo-2-dimethylacetamidoacetate
ethyl 2-bromo-3-dimethylacetamidopropionate
ethyl 2-bromo-4-dimethylacetamidobutyrate
ethyl 2-bromo-5-dimethylacetamidovalerate
ethyl 3-bromo-4-dimethylacetamidobutyrate
ethyl 2-bromo-5-dimethylacetamidovalerate
ethyl 3-bromo-5-dimethylacetamidovalerate
ethyl 4-bromo-5-dimethylacetamidovalerate

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EXAMPLE 11

When the procedure of Example 3 is followed and 2-bromopropionate is replaced by the compounds of Table IV below, then the corresponding product is obtained.

Table IV

ethyl 2-bromoacetate
ethyl 2-bromopropionate
ethyl 2-bromobutyrate, ethyl 3-bromobutyrate
ethyl 2-bromovalerate
ethyl 2-bromo-3-methylvalerate
ethyl 3-bromovalerate
N,N-dimethyl-2-bromopropionamide
N,N-dimethyl-2-bromobutyramide
N,N-dimethyl-2-bromovaleramide,
N,N-dimethyl-3-bromovaleramide

When methyl 4-bromobutyrate of Example 5, Step D is replaced by the compounds of Table IV above, then the corresponding product is prepared.

EXAMPLE 12

When the procedures of Example 3, 9, 10 and 11 are followed and o-cresol is replaced by the compounds of Table II below, then the corresponding product is prepared.

Table II

o-cresol, m-cresol, p-cresol
o-mercaptotoluene, m-mercaptotoluene, p-mercaptotoluene
3-hydroxy-4-carbethoxytoluene
3-hydroxy-4-dimethylcarbamylytoluene
3-hydroxy-4-dimethylcarbamylylmethyltoluene

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3-hydroxy-5-dimethylcarbamyloxymethyltoluene
 3-mercapto-4-carbomethoxymethyltoluene
 3-mercapto-4-dimethylcarbamyloxymethyltoluene
 3-mercapto-4-dimethylcarbamyloxymethyltoluene
 3-mercapto-5-dimethylcarbamyloxymethyltoluene
 methyl 4-methylsalicylate, methyl 3-methylsalicylate

When the procedure of Example 3 is followed and o-cresol is replaced by 5-methylresorcinol, 4-methylresorcinol or methylhydroquinone, then the corresponding products are prepared.

EXAMPLE 13

When p-hydroxybenzaldehyde of Example 1 is replaced with the compounds of Table III below, then the corresponding product is prepared when following the examples of this invention.

Table III

o-hydroxybenzaldehyde, o-mercaptobenzaldehyde
 m-hydroxybenzaldehyde, m-mercaptobenzaldehyde
 3-methyl-4-hydroxybenzaldehyde
 3-carbomethoxy-4-hydroxybenzaldehyde
 3-carbomethoxymethoxy-4-hydroxybenzaldehyde
 2-carbomethoxymethoxy-4-hydroxybenzaldehyde
 3-carbomethoxyethoxy-4-hydroxybenzaldehyde
 3-dimethylcarbamyloxymethyl-4-hydroxybenzaldehyde
 3-dimethylcarbamyloxymethoxy-4-hydroxybenzaldehyde
 3-dimethylcarbamyloxymethylthio-4-hydroxybenzaldehyde
 3-dimethylcarbamyloxymethylamino-4-hydroxybenzaldehyde

EXAMPLE 14

3-((1-[3-(3-(2-(quinolin-2-yl)ethenyl)phenoxy)benzyl]-1-[N,N-dimethylcarbamyloxymethylthio)methyl]thio)propionic acid

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A. 3-[1-carbomethoxyethylthio-1-(N,N-diethylcarbamyloethylthio)methyl]benzaldehyde

A solution of isophthalaldehyde (0.1 mol), N,N-dimethyl 3-mercaptopropionamide (0.1 mol), thiolacetic acid (0.1 mol) and p-tosic acid (0.01 mol) in 100 mL of CH_2Cl_2 are stirred for 24 hr. The reaction mixture is washed with water, dried and evaporated to dryness. The crude product is purified by flash chromatography. The product thus obtained (0.05 mol) is treated with 0.05 mol of sodium methoxide in the presence of 0.06 mol of methyl acrylate in 50 mL of methanol. After evaporation of solvent, the crude product is purified by flash chromatography to give 3-[1-carbomethoxyethylthio-1-(N,N-diethylcarbamyloethylthio)methyl]benzaldehyde.

B. 3-[1-carbomethoxyethylthio-1-(N,N-dimethylcarbamyloethylthio)methyl]benzyl chloride

The aldehyde obtained from Step A (0.05 mol) is 100 mL of EtOH is treated with 0.02 mol of NaBH_4 at 5°C for 1 hr. Excess hydride is decomposed with dilute acid followed by extraction with ethyl acetate. The organic solution is dried and evaporated to dryness. The crude product thus obtained is 50 mL of CH_2Cl_2 is treated with thionyl chloride to give 3-[1-carbomethoxyethylthio-1-(N,N-dimethylcarbamyloethylthio)methyl]benzyl chloride which is used directly in the next step.

C. 3-((1-[3-(3-(2-(quinolin-2-yl)ethenyl)phenoxy)benzyl]-1-(N,N-dimethylcarbamyloethylthio)methyl)thio)propionic acid

A mixture of 4-(2-(quinolin-2-yl)ethenyl)phenol (0.01 mol), the benzyl chloride derivative of Step B (0.01 mol) obtained above and K_2CO_3 (0.012 mol) in 50 mL of DMF is

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heated at 50°C overnight. The reaction mixture is poured into water and extracted with ethyl acetate. After evaporation of solvent, the crude product is purified by flash chromatography. The purified compound is then hydrolyzed with 1.1 equiv of NaOH solution for 2hr. The reaction mixture is then acidified and extracted into ethyl acetate. The organic solution is dried and evaporated to dryness. Purification by flash chromatography gives 3-((1-[3-(3-(2-(quinolin-2-yl)ethenyl)phenoxy)benzyl]-1-[N,N-dimethylcarbamylethylthio]methyl)thio)propionic acid.

When 3-mercaptopropionate in Step D is replaced by the compound of Table V then the corresponding product is prepared.

Table V

ethyl 3-mercaptopropionate
methyl 2-mercaptopropionate
methyl 3-mercaptopropionate
methyl 4-mercaptobutyrate
methyl 3-mercaptobutyrate
2-mercapto-N,N-dimethylpropionamide
3-mercapto-N,N-dimethylbutyramide
3-mercapto-N,N-diethylpropionamide

When N,N-dimethyl 3-mercaptopropionamide in Step A is replaced by the compounds of Table VI the corresponding product is prepared.

Table VI

N,N-dimethyl-2-mercaptoacetamide
N,N-dimethyl-3-mercaptoacetamide
N,N-diethyl-3-mercaptoacetamide
N,N-dimethyl-4-mercaptobutyramide

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When thioacetic acid in Step A is replaced by the compound of Table VII the corresponding product is obtained.

Table VII

thioacetic acid
3-thiopropionic acid
4-thiobutyric acid
3-thiobutyric acid
2-thiopropionic acid

When the procedure of Example 14 is followed and the starting materials are selected from Tables VI and VII then the corresponding product is obtained.

EXAMPLE 15

When quinaldine of Example 1 is replaced by the quinolines of Table VIII below, then the corresponding product is obtained throughout this application.

Table VIII

quinaldine
5-chloroquinaldine
6-chloroquinaldine
7-chloroquinaldine
6-bromoquinaldine
7-bromoquinaldine
7-fluoroquinaldine
6-fluoroquinaldine
5-trifluoromethyl
7-trifluoromethyl
6,7-dechloroquinaldine
6-methylquinaldine
7-5-butylquinaldine

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EXAMPLE 16

The following compounds of this invention are prepared according to the methods described above using analogous reaction condition and starting materials, which are commercially available or prepared according to known literature procedures.

cis-[4-(2-(Quinolin-2-yl)ethenyl)-3'-(tetrazol-5-yl)]stilbene
(M.P. 189-193°C)

CALC: C, 77.79; H, 4.77; N, 17.44

FOUND: C, 74.52; H, 4.93; N, 16.88

CALC: C, 74.45; H, 5.05; N, 16.69 (as Hydrate)

trans-[4-(2-(Quinolin-2-yl)ethenyl)-3'-(tetrazol-5-yl)]-
stilbene
(M.P. 165-169°C)

CALC: C, 77.79; H, 4.77; N, 17.44

FOUND: C, 72.67; H, 4.81; N, 16.99

CALC: C, 72.88; H, 5.17; N, 16.34 (as 1.5 Hydrate)

5-(2-[4-(2-(7-Chloroquinolin-2-yl)ethenyl)phenoxy)methyl]-
benzyl) tetrazole (M.P. 245°C)

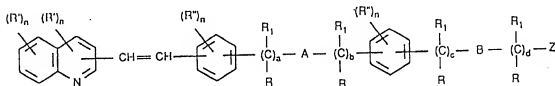
CALC: C, 68.80; H, 4.44; N, 15.43

FOUND: C, 60.28; H, 4.58; N, 13.70

CALC: C, 60.41; H, 5.26; N, 13.55 (as 3.5 Hydrate)

We Claim:

1. A compound of the formula



where

R' is independently hydrogen,
alkyl,
hydroxy,
alkoxy,
carboxy,
carbalkoxy,
halo,
nitro,
haloalkyl,
cyano or
acyl;

R₁ is independently hydrogen,
alkyl or
aralkyl;

R is independently $-(CH_2)_x-X$; $-O(CH_2)_x-X$ (when not geminal
to A or B when A or B is O);
 $-S-(CH_2)_x-X$ or $-NR_1-(CH_2)_x-X$
where x is 0-3 and

X is hydrogen,
alkyl,
aryl,
hydroxy,
alkoxy,
acylamino,

$\begin{array}{c} \text{O} \\ \parallel \\ -\text{CNR}_1\text{R}_1, \end{array}$
 $\begin{array}{c} \text{O} \\ \parallel \\ -\text{COR}_1, \end{array}$
 $-\text{CN}$ or
 tetrazolyl;

R'' is hydrogen,
 hydroxy,
 alkoxy,
 halo,
 haloalkyl,
 $-\text{CH}_2\text{R}$; R or
 $-\text{CH}_2-\text{O}-(\text{CH}_2)_x-\text{X}$;

vicinal R groups together may be $(\text{CH}_2)_y$ - where y is 1-4,
 this forming a 3-6 membered ring;

geminal R_1 and R groups together may form a spiro
 substituent,

$-(\text{CH})_z-$, where z is 2 to 5;

geminal R_1 or R_1 and R groups may together form an

alkylidenyl substituent $\begin{array}{c} \text{CHR}_1 \\ \parallel \end{array}$

A is $-\text{O}-$,

$-\text{S}-$,

$-\text{SO}-$,

$-\text{SO}-$,

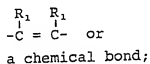
$-\text{NR}_1-$,

$\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-, \end{array}$

$\begin{array}{c} \text{R}_1 \text{ O} \\ | \parallel \\ -\text{N}-\text{C}, \end{array}$

$\begin{array}{c} \text{O} \text{ R}_1 \\ \parallel | \\ -\text{C}-\text{N}-, \end{array}$

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B is -O-,

-S-,

-NR₁-,

a chemical bond;

a is 0-2; where a+b = 1 or 2;

b is 0-2; where a+b = 1 or 2;

c is 0-3;

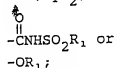
d is 0-3;

n is 0-2;

Z is tetrazolyl,

substituted tetrazolyl where the substituent may be
alkyl, carboxyalkyl or carbalkoxyalkyl; orwhere Y is -COOR₁,

-CN,



and pharmaceutically acceptable salts thereof.

2. A compound according to Claim 1 where the substitution of the side chain is at the 2-position of the quinoline ring.
3. A compound according to Claim 2 where one of R is

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where on of R is $-(CH_2)_x-X$; $-S-(CH_2)_x-X$; $-O-(CH_2)_x-X$
 (when not geminal to A or B when A or B is O);
 $-NR_1-(CH_2)_x-X$ or one or R' is $-CH_2-O-(CH_2)_x-X$
 $-CH_2R$; and R' is hydrogen or halo

4. A compound according to Claim 3 where Y is
 Y is $-COOR_1$;
 O
 $-CN(R_1)_2$ or
 tetrazolyl.
5. A compound according to Claim 4 where R' is 7-bromo or 7-chloro.
6. A compound according to Claim 4 which is 3-((1-[3-(3-(2-(quinolin-2-yl)ethenyl)phenoxy)benzyl]-1-[N,N-dimethylcarbamylethylthio]methyl)thio)propionic acid.
7. A compound according to Claim 5 which is 3-((1-[3-(3-(2-(7-bromoquinolin-2-yl)ethenyl)phenoxy)benzyl]-1-[N,N-dimethylcarbamylethylthio]methyl)thio)propionic acid.
8. A compound according to Claim 5 which is 3-((1-[3-(3-(2-(7-chloroquinolin-2-yl)ethenyl)phenoxy)benzyl]-1-[N,N-dimethylcarbamylethylthio]methyl)thio)propionic acid.
9. A compound according to Claim 5 which is 3-((1-[3-(3-(2-(7-chloroquinolin-2-yl)ethenyl)phenoxy)benzyl]-1-[N,N-diethylcarbamylethylthio]methyl)thio)propionic acid.
10. A compound according to Claim 5 which is 3-[2-(3-(2-(7-chloroquinolin-2-yl)ethenyl)phenyl)-1-(2-carboxymethoxyethyl)thio-2-hydroxyethyl]phenoxyacetic acid.
11. A compound according to Claim 4 which is o-[4-(2-

(quinolin-2-yl)ethenyl)-2-(3-carboxypropoxy)-
phenoxymethyl]-phenoxyacetic acid.

12. A compound according to Claim 5 which is 4-(2-(4-(2-(7-chloroquinolin-2-yl)ethenyl)phenoxymethyl)phenoxy-4-carboxybutyric acid.
13. A compound according to Claim 5 which is 2-hydroxy-3-((2-carboxyethyl)thio)-3-[(2-(4-(2-(7-chloroquinolin-2-yl)ethenyl)phenoxymethyl)phenyl]propionic acid.
14. A compound according to Claim 5 which is 3-[2-(3-(2-(7-chloroquinolin-2-yl)ethenyl)phenyl)-1-hydroxy-2-((2-carboxyethyl)thio)ethyl]phenoxyacetic acid.
15. A method for the treatment of hypersensitive ailments in humans and mammals comprising administering thereto an effective amount of a compound of the formula according to Claim 1.
16. A pharmaceutical composition wherein the active ingredient is a compound according to Claim 1 in admixture with a pharmaceutical carrier.

INTERNATIONAL SEARCH REPORT

International Appl. No. PCT/US89/02692

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) * According to International Patent Classification (IPC) or to both National Classification and IPC IPC(4): C07D 215/12; 215/14; 215/22; 401/10 U.S.C.I.: 546/168; 546/170; 546/172; 546/175; 514/311														
II. FIELDS SEARCHED <table border="1"> <tr> <th colspan="2">Minimum Documentation Searched ?</th> </tr> <tr> <th>Classification System</th> <th>Classification Symbols</th> </tr> <tr> <td>U.S.</td> <td>546/168; 546/170; 546/172; 546/175; 514/311</td> </tr> </table> <p>Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched *</p>			Minimum Documentation Searched ?		Classification System	Classification Symbols	U.S.	546/168; 546/170; 546/172; 546/175; 514/311						
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III. DOCUMENTS CONSIDERED TO BE RELEVANT * <table border="1"> <tr> <th>Category *</th> <th>Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th>Relevant to Claim No. ¹³</th> </tr> <tr> <td>A</td> <td>US, A, 4,661,499 (YOUNG) published 28 April 1987 See entire document.</td> <td>1-16</td> </tr> <tr> <td>A</td> <td>EP, A, 0,206,751 (YOUNG) published 30 December 1986. See entire document.</td> <td>1-16</td> </tr> <tr> <td>A</td> <td>US, A, 4,769,461 (MUSSEY) published 16 September 1988. See entire document.</td> <td>1-16</td> </tr> </table>			Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	A	US, A, 4,661,499 (YOUNG) published 28 April 1987 See entire document.	1-16	A	EP, A, 0,206,751 (YOUNG) published 30 December 1986. See entire document.	1-16	A	US, A, 4,769,461 (MUSSEY) published 16 September 1988. See entire document.	1-16
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<p>* Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the publication but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"A" document member of the same patent family</p>														
IV. CERTIFICATION <table border="1"> <tr> <td>Date of the Actual Completion of the International Search</td> <td>Date of Mailing of this International Search Report</td> </tr> <tr> <td>1 SEPTEMBER 1989</td> <td>27 SEP 1989</td> </tr> <tr> <td>International Searching Authority</td> <td>Signature of Authorized Officer</td> </tr> <tr> <td>ISA/US</td> <td>David B. Springer</td> </tr> </table>			Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	1 SEPTEMBER 1989	27 SEP 1989	International Searching Authority	Signature of Authorized Officer	ISA/US	David B. Springer				
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